IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of	:	Kohn, *et al.*
Serial No.	:	08/225,478
Filed:	:	April 8, 1994
For	:	Gene Therapy by Administration of Genetically Engineered CD34+ Cells Obtained from Cord Blood
Group	:	1804
Examiner	:	Milne

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

In response to the Final Rejection dated June 7, 1996, reconsideration of the above-identified application is hereby respectfully requested.

The claims stand rejected under 35 U.S.C. 103 as being unpatentable over Anderson taken with Moritz and Kohn. This rejection is respectfully traversed.

Applicants' invention is directed to a method of providing a therapeutic effect in a human patient by administering autologous CD34+ cells obtained from cord blood to the patient. The CD34+ cells have been genetically engineered to include at least one nucleic acid sequence encoding a therapeutic agent. The autologous CD34+ cells are administered in an amount effective to provide the patient with an effective amount of the therapeutic agent by expression of the nucleic acid sequence in the patient.

Applicants discovered that the number of circulating hematopoietic progenitor cells drops to levels seen in older children and adults within two days of birth, and that the collection of cord blood cells at birth enables one to obtain increased quantities of cells such as CD34+ cells, which are useful in gene therapy when genetically engineered to include a nucleic acid sequence encoding a therapeutic agent. Applicants also are the first ones to demonstrate that one can obtain CD34+ cells from cord blood of a patient, genetically engineer such CD34+ cells to include at least one nucleic acid sequence encoding a therapeutic agent, and return such genetically engineered CD34+ cells to the circulatory system of the patient, whereby the genetically engineered cells

express therapeutic amounts of the therapeutic agent *in vivo*. Although the cited prior art discloses the genetic engineering of CD34+ cells, the prior art does not disclose or suggest to one of ordinary skill in the art that one may obtain the CD34+ cells from cord blood, genetically engineer the CD34+ cells obtained from cord blood and then administer such genetically engineered CD34+ cells to a patient to provide a therapeutic effect in the patient. At best, the cited prior art renders it obvious to attempt Applicants' claimed method. The case law is clear, however, that such a standard is improper for rendering an invention obvious within the meaning of 35 U.S.C. 103.

Although Anderson discloses the administration of T-cells genetically engineered with the adenosine deaminase gene to human patients in order to treat severe combined immune deficiency, Anderson provides no guidance for one of ordinary skill in the art to administer to a patient genetically engineered autologous CD34+ cells. Anderson discloses a possibility that an enriched population of CD34+ cells may be transduced with an adenosine deaminase gene; however, Anderson provides no guidance as to how this may be accomplished. Furthermore, Anderson provides no suggestion that the CD34+ cells may be obtained for cord blood. Thus Anderson at best provides sheer speculation that one may obtain autologous CD34+ cells from cord blood, genetically engineer such cells, and administer such cells to a human patient to provide a therapeutic effect. Such speculation does not provide a reasonable expectation of success, and therefore does not render Applicants' claimed invention obvious to one of ordinary skill in the art.

Moritz is directed solely to the *in vitro* transfection of cord blood cells with retroviral vectors including the adenosine deaminase gene. The cells may be cultured in the presence of C-kit ligand and Interleukin-6. Moritz, however, does not suggest to one of ordinary skill in the art that CD34+ cells may be separated from other cord blood cells prior to the transduction of the cells. Moritz also does not even remotely suggest to one of ordinary skill in the art that CD34+ cells may be obtained from cord blood, be genetically engineered with at least one nucleic acid sequence encoding a therapeutic agent, and be administered *in vivo* to a human patient to provide a therapeutic effect.

Kohn obtains CD34+ cells from bone marrow as opposed to cord blood. Kohn then cultures the cells in the presence of Interleukin-1, Interleukin-3, Interleukin-6, and human mast cell growth factor. Although Kohn states that culturing the CD34+ cells in the presence of the

above-mentioned growth factors, Kohn provides no suggestion to one of ordinary skill in the art that such transduced CD34+ cells may be administered *in vivo* to a human patient in order to provide a therapeutic effect.

In addition, as mentioned hereinabove, Kohn obtains CD34+ cells from bone marrow. Kohn provides no suggestion of Applicant's discovery that by collecting cord blood, one can obtain increased quantities of CD34+ cells for the genetic engineering thereof. Thus Kohn provides no teaching of how to obtain increased quantities of CD34+ cells, nor does Kohn teach the administration of genetically engineered CD34+ cells to a human patient in order to provide a therapeutic effect. Therefore, Kohn provides no basis for the claimed invention to one of ordinary skill in the art.

The combination of Anderson, Moritz, and Kohn clearly provides no basis for one of ordinary skill in the art to obtain CD34+ cells from cord blood, genetically engineer such CD34+ cells with at least one nucleic acid sequence encoding a therapeutic agent, and administer such genetically engineered CD34+ cells to a human patient in order to provide a therapeutic effect. Kohn and Moritz are directed solely to the *in vitro* transduction of CD34+ cells. Only one reference, Anderson, teaches the *in vivo* administration of genetically engineered cells in order to provide a therapeutic effect. The genetically engineered cells in Anderson, however, are mature T-cells. Such cells are not CD34+ cells. Anderson merely speculates that one could genetically engineer a cell fraction highly enriched in CD34+ cells. Anderson does not, however, suggest that such cells may be obtained from cord blood. Therefore, the combination of Anderson with Moritz and Kohn at best provides sheer speculation that one skilled in the art can obtain CD34+ cells from cord blood, genetically engineer such CD34+ cells with at least one nucleic acid sequence encoding a therapeutic agent, and administer such genetically engineered autologous CD34+ cells to a patient in order to provide a therapeutic effect. At best, such speculation renders it obvious to try to practice the claimed invention, but does not provide one of ordinary skill in the art with a reasonable expectation of success. Therefore, Anderson, Moritz, and Kohn do not render Applicants' invention obvious to one of ordinary skill in the art, and it is therefore respectfully requested that the rejection under 35 U.S.C. 103 be reconsidered and withdrawn.

The claims stand rejected under 35 U.S.C. 112, first paragraph for failing to provide an enabling disclosure. This rejection is respectfully traversed.

The Examiner is basing his rejection upon what he perceives is the lack of predictability in the art of gene therapy. The Examiner also states that the genetically engineered CD34+ cells in Example 2 are not the sole source of therapeutic results in the patients.

In response, Applicants state that the quotations in Marshall relied upon by the Examiner to assert the unpredictability of gene therapy do not state that gene therapy is not effective or will not be effective. The burden is upon the Examiner to show the Applicants' claimed method would not be effective in treating a human patient, not upon the Applicants to prove that the claimed method is effective. In fact, the Marshall article, at Page 1053, states that there are 107 clinical trials that have been approved by the NIH Recombinant DNA Advisory Committee. Thus, one skilled in the art, based upon his or her knowledge of existing gene therapy protocols undergoing clinical trials, would expert reasonably, upon reading Applicants' disclosure, that Applicants' claimed method would be successful. Thus, the Examiner has not proven that the specification does not provide an enabling disclosure.

In response to the Examiner's statement that the genetically engineered CD34+ cells are not the sole source of therapeutic results in the patients in Example 2, Applicants assert that they need not show that the genetically engineered CD34+ cells are the sole source of adenosine deaminase. As stated previously, PCR analyses of peripheral blood samples of the children treated in Example 2 showed that each child has circulating leukocytes which contain the adenosine deaminase gene. Therefore, one skilled in the art would expect reasonably that adenosine deaminase is being expressed by such cells. Applicants need not show that a certain amount of adenosine deaminase is being expressed. The case law is clear that Applicants do not have to show that the administration of the genetically engineered CD34+ cells obtained from cord blood will be effective in humans. (See In Re Anthony, 162 U.S.P.Q. 594 (C.C.P.A. 1969)).

Applicants' have proven the principle that one may administer autologous genetically engineered CD34+ cells to a patient and achieve *in vivo* expression of a therapeutic agent. The Examiner has provided no evidence which would prove that one skilled in the art could not obtain CD34+ cells from cord blood, genetically engineer such CD34+ cells with at least one nucleic acid sequence encoding a therapeutic agent, and administer such genetically engineered autologous CD34+ cells to a patient to provide a therapeutic effect. Applicants, therefore, through their

disclosure, have enabled one skilled in the art to practice the claimed invention. For the above reasons and others, the specification provides an enabling disclosure, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,

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